Review

The Role of RANKL and Involvement of Cementum in Orthodontic Root Resorption

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Abstract: Orthodontic root resorption (ORR) is an unintended side effect of orthodontic treatment, and severe ORR can affect treatment outcome. Receptor activator of nuclear factor kappa-B ligand (RANKL) has been detected in the resorbed cementum and periodontal (PDL) tissues exposed to excessive orthodontic forces. Recent studies have demonstrated that PDL cells and cementoblasts express RANKL that may play a role in ORR during orthodontic tooth movement. It is known that the hardness of cementum in human maxillary premolars differs among individuals. Furthermore, this difference has been reported to be attributed to differences in the calcium (Ca)/phosphorus (P) ratio. A correlation was observed between the Vickers hardness and Ca/P ratio of the cementum in the apical region. These findings suggest that cementum hardness and the Ca/P ratio may be indirectly involved in ORR caused by orthodontic forces. In this review, it aims to identify the role of RANKL and involvement of cementum in ORR.

Keywords: orthodontic root resorption; RANKL; cementum; orthodontic tooth movement

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1. Introduction

Orthodontic root resorption (ORR) was first described in 1914 by Ottolengui [1]. It is characterized by surface resorption with a loss of cementum that is irreversible when the dentin is involved [2]. Several studies have examined the etiology and mechanism of ORR. In an epidemiological study conducted by Kaley and Phillips [3], all patients who underwent comprehensive orthodontic treatment presented with root shortening, and 3% of all patients with severe root resorption (shortening by more than one-quarter of the root length) presented with root shortening in the maxillary central incisors.

The receptor activator of nuclear factor-kappa-B ligand (RANKL), and its two receptors RANK and osteoprotegerin (OPG), are known to be involved in the process of bone remodeling [4]. The RANKL/RANK/OPG system plays an essential role in the induction of bone remodeling. RANKL is a downstream regulator of the formation and activation of osteoclasts, through which many hormones and cytokines exert their bone resorptive effect. RANKL is expressed in the osteoblast cell lineage, and it exerts its effect by binding to the RANK receptor on osteoclasts. This binding leads to a rapid differentiation of the hematopoietic osteoclast precursors into mature osteoclasts. Numerous studies have investigated the cause and mechanism of ORR; in vitro and in vivo studies have reported that RANKL expression in periodontal (PDL) cells plays a significant role in the occurrence of ORR. Recent studies reported that cementoblasts also produced RANKL in response to compressive force and are involved in the ORR.

Recent studies in humans have reported the presence of individual differences in the hardness of cementum near the apex and particularly the calcium (Ca)/phosphorus (P) ratio. A correlation was observed between the Vickers hardness and Ca/P ratio of the cementum in the apical region [5–7]. These findings suggest that the cementum hardness

and the Ca/P ratio may be involved in the occurrence of ORR. In this paper, it aims to review the role of RANKL and the involvement of cementum in ORR.

2. Information Sources and Literature Search

Although this review is not a systematic review, PubMed was searched up to February 2021. Searches were undertaken with no restrictions on year, publication status, or language. The key word and their combinations used for articles' search were: orthodontic root resorption, RANKL, cementum, periodontal ligament, orthodontic tooth movement. Furthermore, the following journals were searched manually: "American Journal of Orthodontics and Dentofacial Orthopedics", "Angle Orthodontists", "European Journal of Orthodontics", Journal of World Federation of Orthodontists, and Journal of Dental Research.

3. Risk Factors of Orthodontic Root Resorption (ORR)

ORR is one of the accidental signs observed during orthodontic treatment: severe ORR can affect the outcome of treatment. Samandara et al. [8] reported that ORR was a multifactorial complication that occurred when multiple (patient- or treatment-related) risk factors overlapped (Figure 1). As presented in Figure 2, if the patient's sensitivity to root resorption is compared to a glass and water, the risk factor (water droplets) drops, and the glass (sensitivity) is gradually filled when orthodontic treatment is started. Root resorption does not occur until the glass is full, but root resorption occurs when it spills (Figure 2).

[Risk factors of ORR]

Patient-related factors

- 1) Genetics
- 2) Sex
- 3) Age
- 4) Tooth type
- 5) Systemic factors
- 6) Root morphology
- 7) History of trauma or previous root resorption

Treatment-related factors

- 1) Appliance type
- 2) Treatment duration
- 3) Type of tooth movement
- 4) Applied force magnitude
- 5) Duration of force application
- 6) Extraction treatment

Others

Figure 1. Risk factors of ORR [8].

Figure 2. The schema of occurrence of ORR. A gradual increase in the number of risk factors (water droplets) following orthodontic treatment slowly leads to root resorption (Figure 2).

4. The Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL) in Bone Resorption and Orthodontic Tooth Movement

RANKL and its receptor RANK are expressed in osteoblasts and the precursor osteoclasts, respectively. They are the key factors that stimulate the formation of osteoclast and osteoclastogenesis [9,10]. RANKL and the macrophage colony-stimulating factor (M-CSF) are involved in the formation of osteoclasts [11]. Osteoprotegerin (OPG), a soluble tumor necrosis factor (TNF) receptor-like molecule, binds to RANK and inhibits RANK/RANKL interactions [12], thereby preventing the differentiation and activation of osteoclasts. Studies in animals using transgenic mice and gene knockout mice have demonstrated that RANK, RANKL, and OPG play a significant role in regulating the formation of osteoclast [13–15].

Kanzaki et al. [16] demonstrated that compressive forces upregulated RANKL expression by induction of COX-2 expression in human PDL cells in vitro. In addition, these forces can increase RANKL and decrease OPG secretion in human PDL cells in vitro [17,18]. Animal studies [19] have demonstrated the expression of RANKL in periodontal tissues during rat experimental tooth movement, and that the extent of experimental tooth movement in rats was accelerated by the transfer of the RANKL gene, and inhibited by the transfer of the OPG gene, to the periodontal tissue [20,21]. The levels of RANKL and OPG in GCF have been found to be increased and decreased, respectively, during experimental orthodontic tooth movement [22]. Therefore, it has been suggested that the RANK/RANKL/OPG system is directly involved in the regulation of orthodontic tooth movement.

5. RANKL Produced by PDL Cells and Cementoblasts in ORR

Previous studies have reported that excessive compressive force enhanced PGE₂, IL-1, IL-6, and TNF- α expression in PDL cells [23–26]. These factors stimulate RANKL expression in hPDL cells. Therefore, it can be concluded that PGE₂, IL-1, IL-6, TNF- α , and RANK play important roles in the orthodontic tooth movement [27–29]. Furthermore, Yamaguchi et al. [22] reported that compressive force resulted in RANKL expression and caused an increase in osteoclastogenesis in vitro. According to Kikuta et al. [28], excessive orthodontic forces stimulated the process of ORR via RANKL and IL-6 expression in hPDL cells. Therefore, PDL cells that are exposed to excessive compressive forces express inflammatory cytokines, which exacerbates the process of ORR.

Recent studies have demonstrated that both PDL cells and cementoblasts express RANKL. Diercke et al. [30] demonstrated that IL-1 β and compressive forces induced significant RANKL expression in cementoblasts. Minato et al. [31] and Iwane et al. [32] reported that exposure of cementoblasts to excessive orthodontic forces leads to the expression of large amounts of RANKL and IL-6, which could induce ORR; therefore, ORR is caused by both PDL cells and cementoblasts. In addition, Yamaguchi et al. [22] reported that ORR could be due to both PDL cells and cementoblasts, probably via RANKL expression in these cells (Figure 3).

Figure 3. The role of RANKL in ORR.

6. Repair of Resorbed Cementum by Cementoblasts

When no more hyaline tissue presents and/or the force level diminishes, the resorption process stops and the repair of cementum starts [33,34]. Initially, the cementoclasts/odontoclasts detached from the resorbed lacunae [35]; they die due to apoptosis [36]. After detachment of cementoclasts/odontoclasts, early cementum repair starts with fibroblast-like cells [33,34]. These fibroblast-like cementoblasts secrete noncollagenous matrix proteins, such as osteopontin and bone sialoprotein, filling the spaces in the residual collagen fibril structure [37]. Subsequently, the cementoblasts secrete collagen fibrils, including a thin cementoid repair matrix [37]. Mineralization ensues with hydroxyapatite crystals development and growth between the collagen fibrils [38], forming reparative cementum of the cellular intrinsic fiber type [39,40].

7. Involvement of Cementum in ORR

7.1. The Hardness of Cementum

As a new attempt, we focused on the relationship between root resorption and cementum hardness from a different perspective. The cementum, which covers the root surface, is composed of thin calcified tissue produced by cementoblasts. The apical third of the root is covered with cellular cementum, whereas the coronary third of the root is covered with noncellular cementum. Active cellular cementum depends on blood circulation. Generally, the mineralized surface of the cementum is more resorbed in the apical part of the root following orthodontic tooth movement than in other regions in humans. Hardness may be a major factor affecting the structure of cementum, particularly during root resorption caused by orthodontic forces.

According to the group of Darendeliler et al. [41–44], substantial individual variations in the occurrence, surface extension, and depth of root resorption have been reported in some studies [41–44]. The hardness (soft, moderate, and hard) and tissue mineral density (TMD) of the cementum in the apical region of the root have been measured using the dynamic micro-indentation method and X-ray μ CT analysis, respectively. The cementum hardness values were lower in the soft and moderate groups than in a hard group [5], and the X-ray μ CT analysis revealed that the teeth in the hard group had higher TMD values than those in the other two groups [6]. Therefore, the hardness of the cementum may be related to the occurrence of ORR. Further studies are necessary to investigate which cementum hardness and TMD contribute to ORR incidence clinically, in animal or human models.

7.2. The Difference of Chemical Composition of Cementum

Rex et al. [45] demonstrated significant individual variations in the hardness of the cementum in the first premolars based on Ca, P, and fluorine (F) concentrations, with a decreasing gradient in these concentrations from the cervical to the apical third of the root. Subsequently, to elucidate the relationship between cementum hardness and degree of resorption, Yao-Umezawa et al. [7] used a pit formation assay to demonstrate that the resorbed area in a soft group was increased to a greater extent than those in the moderate and hard groups.

Scanning electron microscopy-energy spectroscopy has gained considerable importance in dental research [46,47]. Yao-Umezawa et al. [7] reported that the Ca/P ratio of the cementum in a soft group was decreased to a greater extent than those in moderate and hard groups. A correlation was observed between the Vickers hardness and Ca/P ratio of cementum in the apical region ($r = 0.741$, $p < 0.01$). Alvarez-Perez et al. [48] reported that the Ca/P ratio of cementum in the apical region ranged between 1.3 and 1.6. Therefore, a low hardness value (soft cementum) may be attributed to a low Ca/P ratio.

Considering the abovementioned results, individual variations in the hardness and Ca/P ratio of cementum may influence the resistance or susceptibility to root resorption and could be involved in root resorption caused by orthodontic forces. Yamaguchi et al. [5] demonstrated a positive correlation between the respective hardness of enamel and cemen-

tum in humans (hardness: $r = 0.551$, $p < 0.01$, and elastic modulus, $r = 0.552$, $p < 0.01$). If cementum hardness can be estimated based on the value of enamel, it may be possible to accurately evaluate the risk of root resorption in each patient during orthodontic treatment. Therefore, orthodontists would be able to predict root resorption and provide an effective and safe treatment. Further studies are needed to elucidate the relationship between the enamel and cementum, particularly regarding their mechanical properties.

8. Is Cementum the Last Bastion against ORR?

Severe root resorption may not necessarily be observed, even after applying heavy force during treatment. On the one hand, Beck and Harris [49] did not show any relationship between root resorption and heavy force. Weiland [50] reported that orthodontic force, up to a magnitude of 200 cN, may not be decisive for root resorption. Brezniak and Wasserstein [2] and Owman-Moll et al. [51] also reported that there was no root resorption difference detected while using low and high forces (50 and 200 g). On the other hand, Paetyangkul et al. [52] established that the distribution of resorbed lacunae was directly related to the magnitude of a force; resorbed lacunae developed more quickly in the case of heavy forces. One of the explanations for these conflicting phenomena may be resistance to cementum hardness. Regarding the degree of tooth root resorption, the greater the amount of RANKL expressed in PDL cells or cementoblasts, the greater the amount of the resorption. Patients with soft cementum have a higher amount of root resorption as compared with patients with hard cementum. Even small amounts of RANKL expressed in response to light orthodontic forces can cause root resorption in soft cementum teeth. Therefore, cementum hardness is one of the factors involved in the development of root resorption and may be the “last bastion” of root resorption (Figure 4). Additional studies are needed to evaluate the relationship between ORR and cementum hardness.

Figure 4. Schematic figure showing the presumed role of cementum in ORR. Despite a similar amount of RANKL expression, teeth with hard cementum may present with less root resorption than those with soft cementum. Thus, hard cementum may be the last defense against ORR.

9. Conclusions

Cementoblasts exposed to orthodontic forces exacerbate ORR via RANKL, while the cementum with higher Ca/P ratio and TMD values may resist against ORR. Additional studies are required to investigate which types of cementum (cementoblasts) contribute to the incidence of ORR clinically, in animal or human models.

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Informed Consent Statement: Written informed consent has been obtained from the patient to publish this paper.

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Abbreviations

ORR, orthodontic root resorption; PDL, periodontal ligament; RANKL, receptor activator of nuclear factor ligand; OTM, orthodontic tooth movement.

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